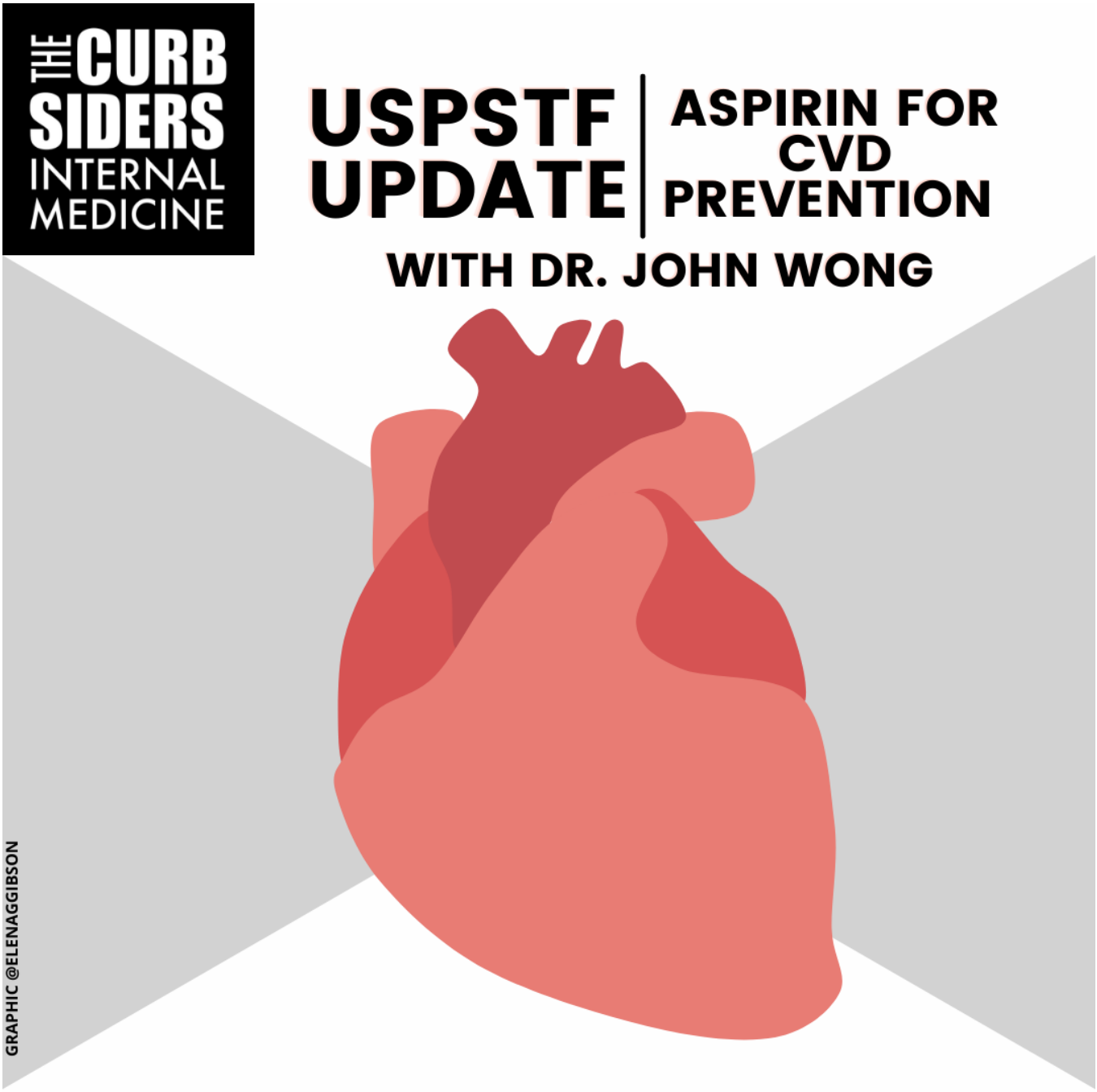
#347 USPSTF Update: Aspirin for Primary Prevention of CVD



[Curbsiders theme]

Paul: All right. This is the part of the show where Matt tries to muster up the appropriate energy to start, and I don't have it in me, but welcome back to The Curbsiders. I am joined by Dr. Elena Gibson.

Elena: Hello.

Paul: [laughs] Hello. Dr. Gibson, how are you?

Elena: That was good.

Paul: Yeah, that was great-

Elena: Great.

Paul: -or high energy, this feels right. [laughs] On tonight's episode, we are discussing the updated USPSTF guidelines with our guest, Dr. John Wong. In just a minute I will let Dr. Gibson tell us more about the guest and the topic. But first, let me remind you what we do. We are The Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice changing knowledge. Elena, tell us about who we talked to and what we talked about?

Elena: Happy to, Paul. We had a great conversation about aspirin use for primary cardiovascular disease prevention with our guest, Dr. John Wong. We talk about the change in recommendations to an age of 40 for initiation of aspirin if their risk is high enough and we talk about the bleeding risks associated with aspirin use. Dr. John Wong, he is a member of the US Preventive Services Task Force, the interim chief scientific officer, vice chair of Academic Affairs, and a primary care internist at Tufts Medical Center and professor of medicine at the Tufts University School of Medicine.

He went to Haverford College and the University of Chicago School of Medicine. He completed an internal medicine residency and a clinical decision-making fellowship at Tufts. And he has been there for the past 40 years making wise decisions.

Paul: All right. Without further ado, let's talk to Dr. Wong.

[Curbsiders theme]

Paul: Hi, Dr. Wong, after much ado and many technical difficulties, we're finally getting started. So, I'd like to thank you for taking the time to talk to us. We usually start by asking our guests to tell us a little bit about themselves. So, if you could just give us a one liner about who you are and what you do, and if you could include at least one fact outside of medicine, that's always appreciated too.

John: Sure. I'm a primary care internist at Tufts Medical Center where I'm also the interim chief scientific officer. In this role, I'm a member of the US Preventive Services Task Force, which I'm a proud

member of. And in terms of about myself, the tagline I like as a doctor comes from my daughter when she was two years old. And she says, "He plays on the computer and eats."

[laughter]

Paul: [unintelligible [00:03:11] on my tombstone.

John: I can imagine it now.

Elena: The basics.

[chuckles]

Elena: Do you play any fun video games, or--?

John: I do not play video games.

[laughter]

John: At least not currently, when my son was much younger, there was something called *Red Alert* that he was very fond.

Elena: Oh, that sounds fun.

[laughter]

Paul: It sounds very cold war. I'm not aware of it.

John: It is. My daughter would play something called *Frogger*.

Elena: *Frogger* is fun.

Paul: Okay, *Frogger*, I have familiarity with.

Elena: That's good.

Paul: All right. Well, that is perfect. So, thank you for spending time with us. And obviously the reason that we've asked you to speak with us is to update us about the new USPSTF guideline for aspirin for primary prevention of cardiovascular disease. So, as per usual, we'd like to start with the case just to frame the discussion. And so, Elena, why don't you tell us about our poor Mr. Young.

Elena: Sure. Nathan Young, he is a 44-year-old male. He has a history of type 2 diabetes, hypertension. He takes some lisinopril. He's presenting for a yearly follow up in clinic. He does not smoke, and he has no history of CVD. But his father and brother both had a history of coronary artery

disease. You calculate his 10-year CVD risk score, and it's 11%. So, before we get to the specifics of Mr. Young's case, why is aspirin use for prevention of CVD considered in these guidelines?

John: So, why aspirin? Well, heart disease and stroke are the leading causes of mortality in the United States, accounting for over one in four deaths. And if you look at how many first strokes and first heart attacks will be expected over the next year, it's over 1.2 million here in the United States. And when you think about prevalence because our focus is on individuals, or patients who have not yet shown the manifestation of cardiovascular disease, so we think about the risk of developing that first stroke or first heart attack. And we think about the group of individuals who have more than a 10% risk. When you think about that, people who are 40 to 49 in the United States have a prevalence of about 2% to 5%. For those who are 50 to 59, the prevalence goes up to 7% to 30% in men and women. And when you go beyond that, the prevalence goes even higher.

Our recommendations focus on people who are 40 to 59 years old, who should have a conversation with their clinician, to see if they're at higher risk for having that first cardiovascular disease event. And if so, whether taking aspirin is right. We call this a grade C, meaning that there's a moderate certainty that aspirin use will have a small net benefit of preventing that first heart attack or first stroke for those who are 10% or higher tenure risk. Now, one way to remember this is to think of a grade C as C for conversation, it's an opportunity to have a conversation.

[crosstalk]

Paul: And, John, for calculating this risk, does USPSTF have a recommendation for a tool to use, is the pooled cohort equation or is there some other? Yeah, how do we get there, I guess, to actually have this discussion?

John: Yes, Paul, as you know there are multiple risk estimators available. The only one that has been validated within the United States is the American College of Cardiology, American Heart Association pooled cohort equation. So that would be an excellent choice. But there are others that could be used, and we do recognize that at times, the pooled cohort equations can overestimate the risk of stroke or heart attack. But there are also populations in which it may underestimate the risk. So, keep in mind that the risks may be higher or lower. And, again, it's an estimate to guide treatment considerations.

Elena: Are there any specific populations where over and underestimates that risk that we know of?

John: Sure. The underestimated risk can sometimes occur in patients from socioeconomically disadvantaged populations. And then one example of where it is overestimated is in healthcare professionals, such as physicians or nurses.

Elena: And thinking of the age, so focusing on that 40 to 59 years, is that any different than the prior recommendations or was that a similar age group?

John: The recommendation is changed dramatically from our last recommendation. The last time we looked at this in 2016, we had a ‘I statement’ for 40 to 49, where there weren't enough individuals in the

studies for us to recommend for or against aspirin for them. And in 50 to 59-year-olds, it was a B recommendation, meaning that we should prescribe aspirin because we felt that the benefits exceeded the risk for harms. And what we have, since those 2016 recommendations are a lot more evidence about the harms of aspirin. Also, three studies in 2018, where aspirin was tested in randomized controlled trials in higher risk populations.

Paul: I do want to get to the risks, because I feel obviously that was one of the things that drove the revision of the guideline. But before we get there, for adults between 40 and 59, can you speak to the extent of the net benefit? Are we talking huge, huge risk reductions that that weren't the conversation, and then we're balancing that against risk? What kind of benefit do we expect from aspirin and the population that we're at least having the discussion?

John: One of the reasons this comes up is when we think about the evidence for benefit, the very first studies about the benefit of aspirin for cardiovascular disease was published in the New England Journal of Medicine back in 1988, as part of the physicians' health study. And that study remarkably showed a 45% reduction in heart attack and stroke, and dying from heart attack and stroke. So, they even published that study prematurely because the evidence was so strong.

Paul: [chuckles]

John: Now, I'm going to fast forward to 2018, when there were three landmark studies published in consecutive months in the New England Journal of Medicine, in The Lancet, and in the New England Journal of Medicine. And those three studies had tens of thousands of individuals in each one. I'm going to spend a little more time talking about the study of patients with diabetes. So clearly, patients with diabetes have a higher risk for cardiovascular disease. I want to point out that the average age of those patients was about 63. And they were followed, on average, almost seven and a half years. So, we're talking about what happens to them in terms of cardiovascular disease. And if it's okay, I'm also going to talk a little bit about what happens to them in terms of harms, so that you can get a picture of the benefits versus the harms.

In patients with diabetes, there was a 12% reduction in what are called composite cardiovascular outcomes. So that includes stroke and heart attack. And all three of these studies use a composite outcome. And there's some slight variations, but think about that is counting the numbers of folks who have a heart attack or a stroke, or who may die from a heart attack or may die from a stroke, excluding those who might have a bleeding event, which could be attributed to aspirin.

In the ASCENT Trial, that's the acronym, they found a 12% reduction in this cardiovascular disease composite outcome. On the harm side, they found roughly a 30% increased risk of a major bleeding event. So, a 12% reduction versus a 30% increase relatively. For every 91 people who are treated with aspirin for their diabetes, you will prevent one of them from having a major cardiovascular event. There is also the number needed to harm where you could do the reciprocal of 0.9%. And you end up with a number needed to harm of 112 individuals. Out of that 112, one of them will have a major bleeding event. So, you're talking 91 versus 112.

Paul: So pretty close.

John: They're pretty close. And, in fact, that conclusion in the New England Journal of Medicine is that that cardiovascular benefit is counterbalanced by that bleeding risk. Pretty close exactly as you say, Paul. Now, that was in 2018. One month later, the ARRIVE study was published in The Lancet. And here, they found no statistically significant reduction benefit from aspirin versus placebo. And this is in a group of patients who had an average ACC/AHA risk of 17%. So, we talked about patients with diabetes, and now we're talking about a moderately high risk or high risk of having a 10-year stroke or heart attack. And so, they found no statistically significant benefit, but they then looked at major bleeding, and what they found was over a twofold increase in gastrointestinal bleeding associated with aspirin use. No cardiovascular benefit, but doubling of the GI bleeding risk.

And that brings me to the last study, which was again published one month later in October of 2018, in the New England Journal of Medicine, where this was an older aged population with a mean age of 74. And they, again, found no statistically significant benefit in preventing cardiovascular disease associated with aspirin. And they found a 30% increased risk of having a major hemorrhagic event. So, we have two studies without cardiovascular benefit, increased bleeding risk in two of them. And then we have a third study, which found a benefit in cardiovascular disease offset by a bleeding risk.

Now, when we as the US Preventive Services Task Force look at the evidence, we look at the totality of the evidence. We're not focused on just those three studies. When we pool together 11 randomized controlled trials involving over 130,000 patients, remember, I said before 45% reduction. What we find now is that there's a 12% reduction in nonfatal heart attacks, a 12% reduction in nonfatal strokes, but no reduction in mortality from heart attacks, no reduction in mortality from stroke. And so over the 45-year period, things have changed.

Elena: And just thinking about this comparison to the 1988 study, is there a thought-- is it statins, better blood pressure management? What changed so much?

John: You're spot on. There have been secular changes over the past 45 years. If you go back to 1988, we had a very limited arsenal of drugs available for treating hypertension, a limited arsenal of drugs or interventions for high cholesterol, we had fewer interventions for helping people stop smoking. And there have been secular changes in terms of getting the word out about being more physically active, about eating a healthier diet. What has happened over the past 45 years, fortunately, is that the underlying risk for having a stroke or heart attack in the general population, again, I'm focusing on the population who have not yet had a stroke or heart attack. That narrowing that improvement in the underlying risk accounts for why the benefit versus the harm from aspirin has narrowed. And consequently, we've changed our recommendations for that.

What I haven't yet spoken about is for the population of patients who are 60 and older. And what that New Zealand studies showed was that even in the absence of aspirin, your bleeding risk increases as you get older. And then what you have to keep in mind when we pool the studies together, 10 studies looking at bleeding risk associated with low-dose aspirin, that bleeding risk was not affected by age as a relative risk. But the absolute risk would be multiplied by that relative risk. So, there was a 60% odds

ratio increase in gastrointestinal bleeding, and a 30% increased risk for intracranial bleeding. And in the New Zealand study, gastrointestinal bleeding was not entirely benign, with 3% to 5% of individuals experiencing mortality from their gastrointestinal bleeding.

When you look, however, at intracranial hemorrhages, those are rarer. The GI bleeds are much more frequent, but the mortality rate can be as high as 70% among those having intracranial hemorrhages. When you look at the balance of deaths related to cardiovascular disease, and the balance of deaths associated with gastrointestinal bleeding, and you look at that in the form of a lifetime computer simulation model, because we don't have a lifetime population that we follow but we can simulate that. What we see is the cardiovascular disease benefit is higher if you start younger. But it is offset to some extent by bleeding risk. And as an individual who has not yet experienced a stroke or a heart attack increases around age 60 and higher, that bleeding risk cancels out the benefit from the cardiovascular disease. We do not recommend starting aspirin to prevent a first heart attack or first stroke for patients in their 60s. Think about those three randomized control trials that I mentioned.

Paul: John, I just want to summarize and recap just one more time. That was a really helpful overview of the voluminous amounts of evidence that we've had how things have evolved and how we got to where we are. But I just want to make sure I'm understanding. So, for adults aged 40 to 59, who have a relatively high 10-year risk or greater than 10% of cardiovascular disease risk, you should at least have the conversation about starting aspirin in this group. There's a small net benefit probably, there is a bleeding risk, but probably up until the age of 60, it sounds like the benefit is might be a little bit more than the risk. And then 60 and older, the other recommendation, it sounds like you've now crossed the threshold where the bleeding risk-- We now know based on some evolving evidence, the bleeding risk probably outweighs any benefit that there is and in fact that the benefit seems to be thrown into question a little bit. So, in this population, the recommendation is against starting aspirin in patients who are over the age of 60 just because the risks of harm outweigh the benefits. Is that a fair summary of what we know so far?

John: I think so. I would just say briefly that we call that a grade D recommendation, and 60 and above, we feel that the harms cancel out the benefit. And just as you can think about grade C as conversation, you can think about grade D as Don't. So, it's important to know that aspirin use has--

Paul: You're right on my level, John. This is great.

John: It's important to know that aspirin uses greater benefit when started at a younger age. But it also comes with some potential serious bleeding harms. And that risk goes up as people age, particularly for those who are 60 and older, and aspirin multiplies that risk.

Paul: Perfect. All right. We have another patient to talk about. Elena, why don't you talk us through?

Elena: I know we've talked a lot about not starting aspirin when someone is 60 or older. So, in this case, we have a 65-year-old gentleman, he has a past medical history of hyperlipidemia. He's on atorvastatin, he also has a 50-pack-year history of smoking tobacco, and he's coming into clinic to establish care. He's been taking one baby aspirin for what he thinks is primary prevention for years.

Someone recommended it, he's not really sure. What is the recommendation if a patient is already taking aspirin for primary prevention? Is there any guidance on stopping it or what does USPSTF think?

John: It's a really important critical point. Our recommendation statement focuses on starting aspirin for the prevention of cardiovascular disease. We know from the NHIS that perhaps one in four people in this nation, 40 and older are taking aspirin. And that perhaps 23% of those are doing so without a clinician recommendation. And perhaps over roughly about 50% of those aged over 70 are doing so. And for those who are doing that it's important for them to know that there are potential serious harms. And so if they haven't had a conversation with their trusted clinician, I would encourage them to have that conversation. Although millions take aspirin without any harm and they take it safely, there is risk for serious harms. And they really need to have a conversation about the benefits versus the harms, because the evidence has changed over the past 45 years, and there's a narrowing of that overall net benefit when you think about benefit versus harms.

Paul: So just to be explicit, because I feel like the fear is, the takeaway might be just no aspirin for patients for primary prevention, which is not what the recommendation is that there is no explicit recommendation to stop aspirin in patients. It's more you should have a conversation about the risks and benefits with your trusted clinician, is that correct?

John: Absolutely. Our recommendation is about starting it. Anybody who's thinking about stopping a medication including aspirin, needs to have that conversation so that they understand why they're receiving or taking the medication. And if they don't know, and haven't had that conversation with their trusted clinician, they need to go ahead and have that conversation because they may not be fully aware of the risk for harm from stopping, as well as starting without having that conversation. So, thanks for highlighting that, Paul.

Paul: Elena, I don't know about your patients, but I'm shocked by the numbers because mine are wildly excited to come off of medications. I feel like I don't have any patients that are [laughs] sneakily taking extra things behind my back, but maybe I'm not asking the right questions, too. I'm staggered that many people are just taking aspirin, though, I guess it makes sense. Since it's had this reputation has been so helpful for so long.

John: We tend to like simple rules, and baby aspirins are available over the counter without a prescription. Once things get out where we think things are beneficial, one of my favorite books is *Predictably Irrational*. It talks about how we think logically, we're making a decision based on logic. And it talks about how, for example, why is it that a one cent headache pill doesn't work, but a 50-cent headache pill will work? And so, it's by Dan Ariely, *Predictably Irrational.* It talks about how we are wired sometimes to make irrational as opposed to what we think we do which are rational decisions.

Elena: That makes me feel better.

Paul: We will add that as a pick of the week.

[laughter]

Elena: So, really briefly, I did want to ask, John, the last recommendation in 2016 discussed aspirin in colorectal cancer prevention. And this recommendation seemed like there was a review of evidence, but then, ultimately, there was no comment on the recommendation. Can you talk a little bit about why that was?

John: Absolutely. So, colorectal cancer prevention was a piece of the 2016 recommendation. In this case, as we did with cardiovascular disease, we looked at new evidence, but we also relooked at studies that have been published. And when we did that, we looked at four randomized control trials up to 10 years. And we found no reduction in colorectal cancer incidents. In 2016, the Women's Health Study found a decrease in colorectal cancer incidence in observational study follow up at 17.5 years. But now that study has 26-year follow up, and they report no persistence of that benefit. We have two randomized control trials that looked at colorectal cancer mortality. One of them found a decrease in colorectal cancer mortality at 18 years. But the other, the Women's Health Study did not find a colorectal cancer reduction.

We've got conflicting data from multiple studies. And so we were uncertain about the benefit that we had observed. Again, it's an example where evidence changes. And it should, because the evidence has changed influence our decisions about what we do for our patients and wisdom.

Paul: Yeah. That'll be an easier sell because I feel that's something that wasn't out there in the ether. I knew somewhere I'd heard at some point, maybe there's a reduction in colorectal cancer risk, but it was not something talked about in terms of the way cardiovascular risk was, so I don't think I've met a patient who's taking an aspirin for their bowels. So, I feel it's probably an easy thing, where we're not going to be really reversing a lot of habits or changing a lot of minds because people think of it that way in the first place. So, it's probably almost easier to have a conversation and makes things a bit simpler to even leave that out of this particular recommendation.

John: The good news is that the Task Force has a number of recommendations for reducing the risk of colorectal cancer through evidence-based screening, whether it'd be through direct visualization or through stool-based test. Anyone who has a concern about their risk for colorectal cancer should have a discussion with their trusted clinician about these other options.

Paul: Dr. Wong, this has all been extraordinarily helpful. I thank you so much for catching us up about the changes and the rationale behind those. I guess if you could summarize for our audience what you hope they will come away from this audience from, that'd be very helpful.

John: The bottom line here is that when you're thinking about cardiovascular disease, think about age, and think about the risk for having a cardiovascular disease event as to whether or not you should or should not start aspirin as part of primary prevention.

[Curbsiders theme]

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Elena: Yummy.

Paul: [laughs] That one delighted me. Get your show notes at *thecurbsiders.com*. And while you're there, sign up for our mailing list to get our weekly show notes in your inbox. Plus, twice each month you'll get our Curbsiders digest, recapping the latest practice changing articles, guidelines, and news in internal medicine.

Elena: We're committed to high value practice changing knowledge, and to do what we need your feedback. So please subscribe, rate, and review the show on Apple Podcasts or Spotify or email us at *thecurbsiders@gmail.com*.

Paul: A special thanks to our writer and producer for this episode Dr. Elena Gibson, and to our whole team. The Curbsiders is produced and edited by the team at Pod Paste. Elizabeth Proto runs our social media, and Stuart Brigham composed our theme music. Until next time, I've been Paul Nelson Williams.

Elena: As always, this is Elena Gibson. Thank you and good night.

[Curbsiders theme ends]

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